Bulletin of Shinshu Honan Women's Junior College

Hypoxic Pulmonary Vascular Reactivity with Advancing Age in Rats

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Despite many investigations, the mechanism of hypoxic pulmonary vasoconstriction (HPVC) has not been clearly elucidated. The hypoxic-pressor response occurs in isolated perfused lung, the basic mechanism of hypoxic vasoconstriction does not require systemic neural of humoral input (1). However, two types of hypotheses have been proposed to explain the main mechanism of HPVC. First, hypoxia may elicit pulmonary vasoconstriction via a direct action on the pulmonary vascular smooth muscle (2). Second, some unknown cell type senses hypoxia and produces and / or releases a constrictive mediator, which then stimulates the smooth muscle to contract (2). There is little information on changes in pulmonary vascular reactivity-induced by aging (3, 4). We now describe an increased pulmonary vascular responses to alveolar hypoxia and Angiotensin II (AII) administration in old rats compared with young rats. The comparison studies were performed with isolated perfused lung with blood. Also, this study was made the measurements of pulmonary and systemic arterial blood pressures at

rest in conscious these rats.

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The lungs were obtained from male Sprague-Dawley (SD) rats with a body weight 520±50 g, obtained as young aged (2-months of age) and old aged (12-months of age). The isolated perfused lung with blood (Fig. 1) was allowed to equilibrate for 20 min under normoxic condition (21.0% O_2, 5.1% CO_2, N_2 Balance) prior to beginning experimentaion. The protocol was identical for each rat lung preparation and was

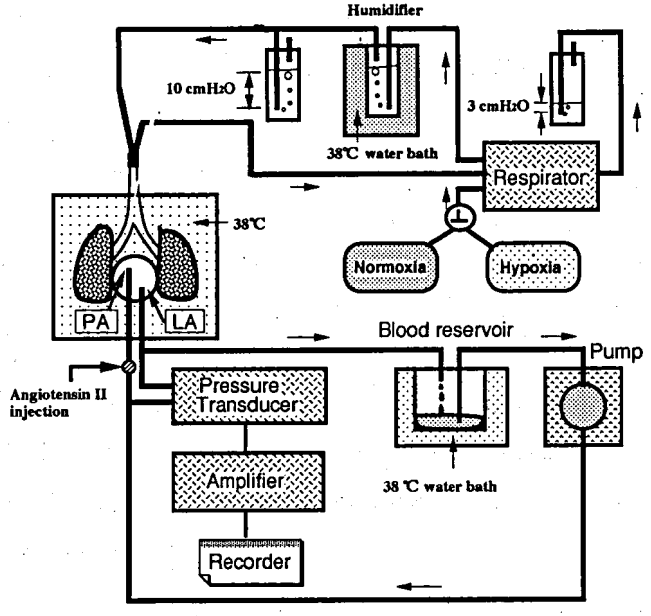

Fig.1 Measurement methods of pulmonary hemodynamics in isolated-perfused rats lungs.
PA:Pulmonary artery, LA:Left atrium, Normoxia : 21.0% O_2, 5.1% CO_2, N_2 Balance, Hypoxia : 3.0 % O_2, 5.1 % CO_2, N_2 Balance

patterned after previous studies (5). A 5 min hypoxix (3% O_2, 5.1% CO_2, N_2 Balance) exposure and 5 min normoxic recovery period was followed by an intra arterial injection of Angiotesin II (AII, Sigma) at a dose of 0.2 μg. The Ppa returned to the baseline level 10 min after AII injection.

On the other hand, male SD rats (old and young aged-rats) weighing 420 to 620 g were anesthetized with ketamine hydrochloride (70 mg/ kg, ip). Hand-made catheters were placed in the carotid artery, jugular veins, and pulmonary artery as previously described (Fig.2,3)(6). Six hours after the catheter placement, rats were studied that mean systemic and pulmonary artery pressures were measured by pressor transducers (Nihon Kohden, TAP-300). After measurements of baseline hemodynamics, all animals were then killed by overdose pentobarbital sodium (50mg/ kg, ip). The ventricle was removed en bloc. following the method of Fulton et al..(7), right ventricular free wall (RV) and left ventricle together with septum (LV+S) were weighed separately.

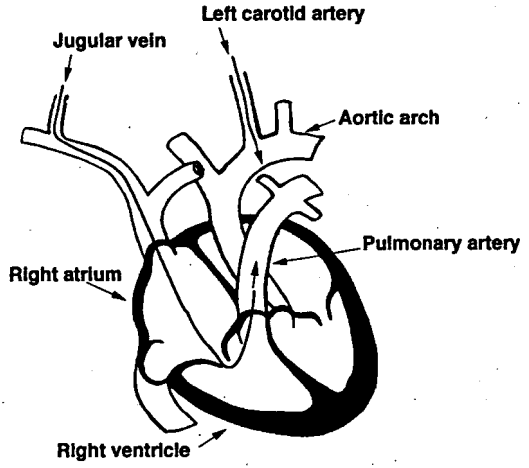

Fig.2 Measurements of pulmonary and systemic arterial blood pressues.

We express their weights as the ratio RV／(LV+S).

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Fig.4 shows the Ppa measured for the old and young groups on

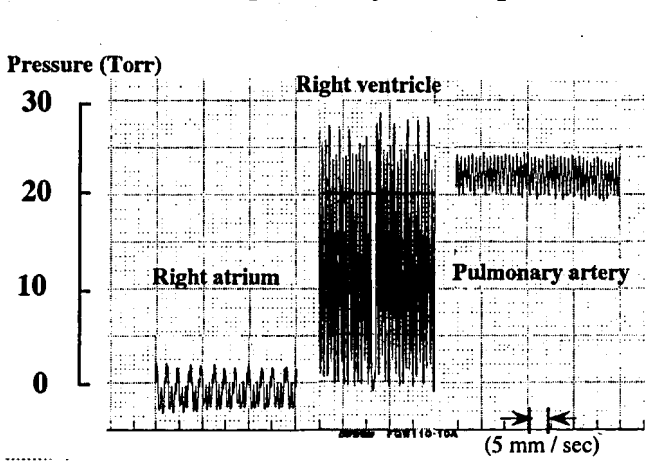

Fig.3 The waves of each blood pressure.

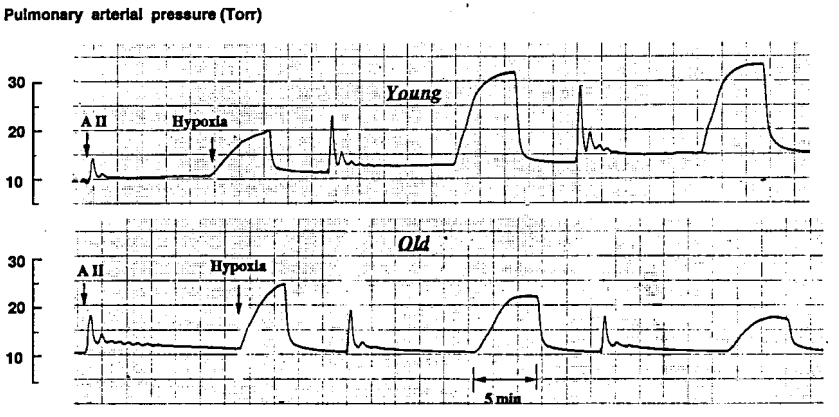

Fig.4 Representative tracings of alternating pulmonary arterial pressure (Ppa) induced by hypoxic and Angiotensin II challenges.

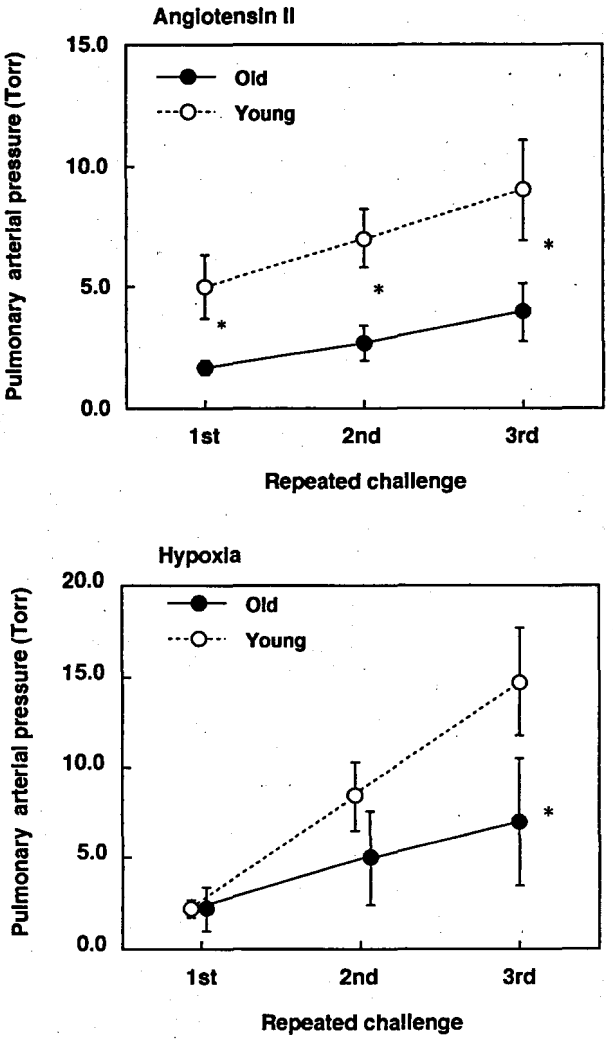

Fig.5 Pulmonary vascular pressor responses to repeated challenges with alveolar-hypoxia and bolus injection of Angiotensin II (0.2 μg/0.1ml saline).
*Statistically significant differences from old rats values ($p<0.05$)

isolated perfused lung with blood. This fig shows an example of three pairs of hypoxic vasoconstriction each time followed by A II and hypoxia-induced vasoconstirictions. Isolated perfused lung from old-age rats had reduced vasoconstriction in comparison with lung from young rats, when exposed alveolar hypoxia. Fig. 5 compares A II-induced pulmonary vasoconstriction in the old and the young groups. Aging enhanced pulmonary vasoreactivity induced by A II. Fig. 6 shows aging factor

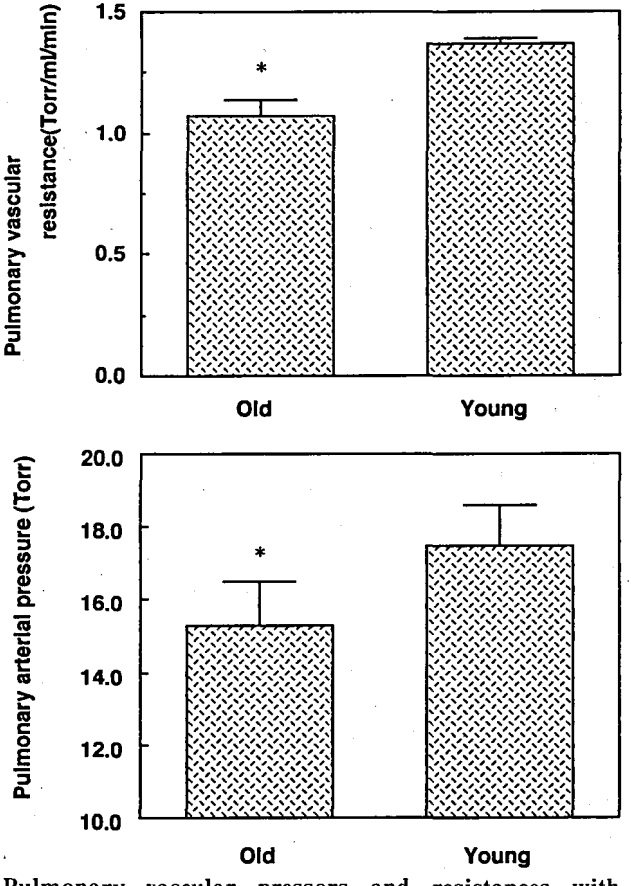

Fig.6 Pulmonary vascular pressors and resistances with alveolar-normoxia in old and young rats. *$p<0.05$

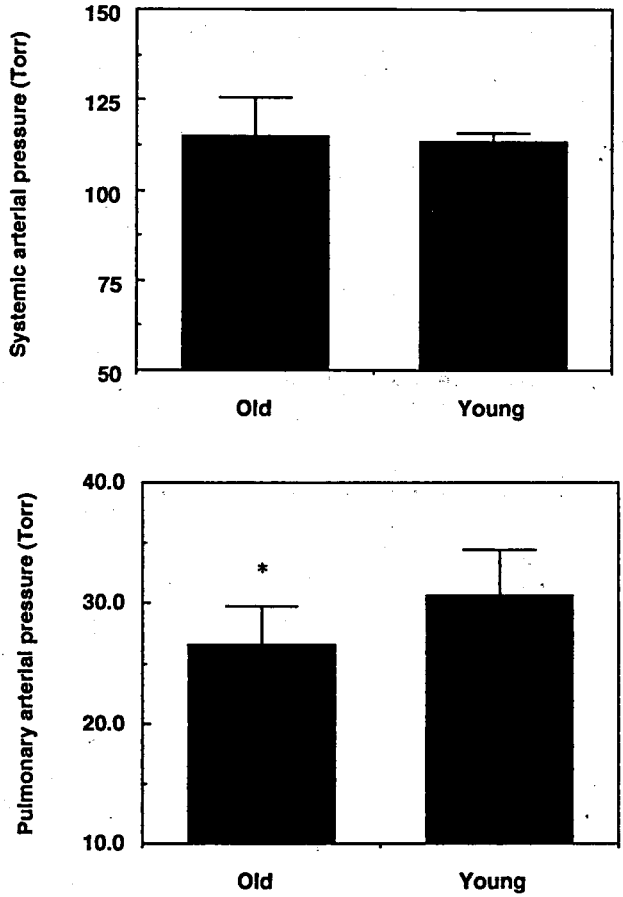

Fig.7 Pulmonary and systemic arterial pressures at rest in conscious old and young rats.
*$p<0.05$

decreased the pulmonary vascular resistance during exposure to normoxia. Figs. 7 and 8 appears, in catheter-implanted rats, aging was decreased the mean pulmonary arterial pressure and pulmonary arterial pressure to systemic arterial pressure ratio (Ppa/ Ppa), while not affecting systemic artery pressure. There were no significant

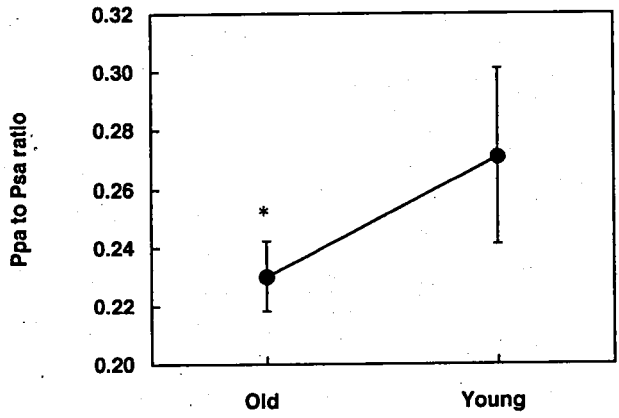

Fig.8 Pulmonary arterial pressure to systemic arterial pressure ratio in conscious old and young rats.
*$p<0.05$

Table 1 Body weights and ventricular weights in old and young rats.

	Old	Young
Body weight(g)	540±8.5	425.5±3.4*
Right ventricle (mg/100g BW)	55.2±2.8	57.7±3.5
Left ventricle with septum (mg/100g BW)	260.0±25.8	261.3±9.4
RV/(LV+S)	0.274±0.030	0.286±0.022

*$p<0.05$ vs.Old rats

changes in the right ventricular weight (RV), left ventricular weight with septum (LV+S) and RV to LV+S ratio (RV/(LV+S)) in old and young rats (Table 1).

* * * * *

In previous investigation, the infant rats will always have fewer arteries than the adults (8). The infant are left with a similar decrease in arterial concentration and increase in medial wall thickness as the adults, they have more peripheral extension of muscle. Older rats had smaller right ventricular hypertrophy than younger, but the younger rats were studied older than our group and perhaps represent an intermediate group in which the response is blunted. There was a tendency for greater impairment of hypoxic pulmonary vasoconstriction in the aging rats. The aging rats exhibited a different morphological response to altitude exposure. Smooth muscle hypertrophy differences between young and aging rats is not apparent. It is apparent that the aging rats exhibited a markedly different pulmonary vascular morphologic response to chronic hypoxia (8).

In contrast to the numerous studies of systemic vessels, the effects of aging on pulmonary vascular responsiveness-induced by hypoxia has been somewhat limited. Fleish and Hooker reported a reduction in the dilation produced by isoproterenol with advancing age in rabbit and rat pulmonary arteries (9). Also, β-adrenoreceptor activity in the rabbit pulmonary artery has been shown to increase with age (10). Blood vessel undergo a number of alterations during the aging process, including in structure (11), enzyme activities (12), and responsiveness to drug (9). A decrease in β-adrenoreceptor activity in arterial smooth muscle with increasing age has been repeatedly demonstrated (12). Also, aortas from 12-month-old rats contracted less to norepinephrine, serotonin, and KCℓ than aortas from 2-month-old rats. Lung isolated

from 12 month-old-rats exhibited reduced vascular response to the vasoconstirctor agents Angiotensin II and hypoxia. The reduced hypoxia-induced pulmonary vasoconstriction in the present aging rats may have been due to a menbrance or metabolic alteration, although the enhanced synthesis and release of a pulmonary vasodilator cannot be discounted (13). The pulmonary vascular hyporeactivity with advancing age is suggested.

The author acknowledge the technical supports of Dr,A.Sakai and Dr, K.Asano.
This study was supported by the Ministry of Education, Science and Culture, Grant-in-Aid for Encouragement of Young Scientists, 1992, No. 04780161.

References

1) Grover R, Eagner WW, McMurtry IF, Reeves JT : Pulmonary circulation. Chapter 4, Handbook of physiology, 1983.

2) Fishman AP:Hypoxia on the pulmonary circulation. How and where it acts. Cir.Res., 38, 221-231, 1976.

3) Tucker A, Greenless KJ, Wright ML, Miglly N : Altered vascular responsiveness in isolated perfused lungs from aging rats. Exper., Lung Res., 3, 29-35, 1982.

4) Tucker A, Miglly N, Wright MKL, Greenless KJ : Pulmonary vascular changes in young and aging rats exposed to 5486 m altitude. Respiration, 46, 245-257, 1984.

5) McMurtry IF, Davidson AB, Reeves JT, Grover RF:Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lung. Cir. Res., 38, 99-194, 1976.

6) Chang S, Sakai A, Voelkel NF : Dibutyryl-cAMP blocks endotoxin-induced lung injury in rats. Am.Rev.Respir.Dis., 140, 1814-1817,

1989.

7) Fulton RM, Hutchinson EC, Hones AM: Ventricular weight in cardiac hypertrophy. Br.Heart J., 14, 413-420, 1952.

8) Rabinovitch M, Walter JG, Olle SM, Lynne R: Age and sex influence on pulmonary hypertension of chronic hypoxia and on recovery. Am.J.Physiol., 240, H62-H72, 1981.

9) Fleish JH,Hooker CF: The relationship between age and relaxation of vascular smooth muscle in the rabbit and rat. Cir.Res., 38, 243-249, 1976.

10) Park MK, Diebl AM, Sunderson JH: Maturation of beta-adrenergic receptor activity of rabbit aorta and pulmonary artery. Life Sci., 19, 331-328, 1976.

11) Tuttle RS: Age-related changes in sensitivity of rat aortic strips to norepinephrine and associated chemical and structural alterations. J.Gerontrol., 21, 510-516, 1966.

12) Kirk JE: Variation with age in the creatine phosphokinase activity of human aortic tissue. J.Gerontrol., 17, 369-372.

13) Cohen ML, Berkowitz : Age-related changes in vascular responsiveness to cyclic nucleotides and contractile agonists. J.Pharmacol. Ex.Therap., 191, 147-155, 1974.

ラットの加齢にともなう低酸素性肺血管収縮反応

桺村　修生

要旨：　本研究は，加齢にともなう低酸素性肺血管収縮の変化について検討することで，中高年層における高地肺水腫発症の危険性を探ることにした。これらを検討するために，ラットも用い摘出潅流肺装置により低酸素およびＡⅡによる肺血管収縮反応を直接的に観察することとした。また，覚醒安静時の肺動脈圧(Ppa)および体血圧(Psa)も測定した。Sprague-Dawleyラットを用い，一方は若年ラット（Y群）の２ケ月令10匹，他方は加齢ラット（O群）の12ケ月令10匹とした。Fig.1に示すような摘出潅流肺装置を用い，肺循環動態を観察するために，肺換気は21.0% O_2，5.1% CO_2，N_2 Balanceにし，Angiotensin Ⅱ (0.2μg／0.1ml)を投与し，10分間の肺血管反応および肺に低酸素ガス（3.1% O_2，5.1% CO_2，N_2 Balance）を５分間換気し肺血管反応をみた。カテーテル挿入による肺動脈圧の測定実験をおこなうため，O群５匹とY群５匹を用いた。PpaおよびPsa測定は，安静時標高760m（辰野町）で行った。Hypoxia換気時およびＡⅡ投与のPpaは，O群がY群より有意（$p<0.05$）に低値を示した。また，PpaおよびPVRは，O群がY群より有意（$P<0.05$）に低値を示した。覚醒時のPpaは，O群がY群より有意（$p<0.05$）に低値を示した。しかし，Psaは，O群とY群の間には有意差がなかった。右心室重量（ＲＶ），左心室重量（ＬＶ＋Ｓ）およびＲＶ／（ＬＶ＋Ｓ）には，O群とY群には差がなかった。しかし，Y群は，O群に比較して右心室肥大の傾向にあった。今回の実験から，低酸素とAngiotensinⅡに対する肺血管収縮反応は，加齢にともない減少することがわかった。このことは，肺血管膜に対する代謝的変化によるかも知れないが，肺血管拡張物質の放出促進とは考えにくく，今後の研究課題としたい。